21. (New) The method of claim 16, wherein the activating ligand is a heregulin-β variant, heregulin agonist antibody, or fragment thereof capable of binding to the HER2 or HER3 receptor, wherein said heregulin-β variant is selected from the group consisting of heregulin-β variants having an amino acid substitution at one or more amino acid residues corresponding to positions S177, H178, L179, V180, K181, E184, E186, K187, T188, V191, N192, G193, G194, E195, M198, V199, K200, D201, N204, P205, S206, R207, Y208, L209, K211, P213, N214, E215, T217, G218, D219, Q222, N223, Y224, M226, S228, and F229 of SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, or of the mature polypeptide within SEQ ID NO: 3.

REMARKS

Claims 1-18 are pending in the application, claim 18 standing withdrawn from consideration. The amendments to the specification correct minor typographical errors (inserting the Greek letter "γ" where it was inadvertently omitted, correcting the spelling of the word "above"). Support for these corrections may be found in the specification as filed, for example, at page 27, line 29 (paragraph 152). The amendments to claims 1-7, 9, and 14-17 find support in the specification and claims as filed. Thus, the amendments to claims 1, 4, 5, 14, and 16 find support, for example, at page 3, lines 40-41 to page 4, lines 1-30 (paragraphs 12-15); page 5, lines 15-17 (paragraph 24); and page 27, lines 29-40 to page 28, lines 1-5 (paragraph 152). The amendments to claims 2, 15, and 17 find support in the specification, for example, at page 27, lines 8-21 (paragraphs 141 through 150). The amendments to claims 3-7 and 9 amend the claim dependency and correct typographical errors.

The new claims 19-21 are directed to subject matter disclosed in the specification as originally filed. For example, new claims 19-21 find support in the specification at page 28, lines 6-23 (paragraphs 153-157). The named heregulin-β variants are described as amino acid substitutions in the mature heregulin-β1 sequence, numbered from serine at position 177, in which at least amino acid residues 207-251 (β1) or 177-221 (β2, β2-like, and β3) are corresponding residues (e.g., serine 207 of Figure 2A-E, SEQ ID NO. 3, corresponds to S177 of the mature heregulin-β1 sequence disclosed at page 28, line 9 (which also corresponds, for example, to serine 177 of Figure 3A-E, SEQ ID NO: 5)).

No new matter is introduced by way of the amendments and new claims.

Applicants respectfully request the reconsideration of the claims 1-12 and 14-17 and consideration of new claims 19-21 in view of the above amendments and the following remarks.

The Rejections to Claims 1, 8, 10, 12, 13, 14, and 16 under 35 U.S.C. § 112 first paragraph

Claims 1, 8, 10, 12, 13, 14, and 16 stand rejected under 35 U.S.C. § 112, first paragraph, the Examiner stating that the specification does not enable a person skilled in the art to use the invention commensurate in scope with these claims. However, Applicants note with appreciation the Examiner's statements that the specification enables one of ordinary skill in the art to use polypeptides of the heregulin family and agonist antibodies thereof in the claimed methods of the invention (page 5, lines 2 and 17-18 of the Office Action mailed 12/06/2002).

Upon entry of the foregoing amendments, the claims are directed to such subject matter; thus the rejections to claims 1, 8, 10, 12, 14, and 16 under 35 U.S.C. § 112 first paragraph should be withdrawn. The rejection to claim 13 is considered to be moot, that claim being cancelled with this amendment.

The Rejections to Claims 4 and 9 under 35 U.S.C. § 112, second paragraph

Claims 4 and 9 stand rejected under 35 U.S.C. § 112, second paragraph as indefinite, claim 4 for reciting the phrase "β2-like" and claim 9 for reciting "an agonist antibody."

The group of activating ligands recited in claim 4 includes a β2-like heregulin polypeptide. A β2-like heregulin polypeptide has an amino acid sequence as disclosed in Figures 5A-5D, SEQ ID NO: 9, and at page 5, lines 8-10 (paragraph 22); page 5, lines 40-41 to page 6, lines 1-4 (paragraph 32). Applicants thus respectfully submit that this disclosure provides definite meaning to the term "β2-like." Accordingly, for at least the reason that the amino acid sequence of β2-like molecules is disclosed in the specification, Applicants respectfully submit that claim 4 satisfies the requirements of 35 U.S.C. § 112, second paragraph.

Claim 9 has been amended to recite "a heregulin agonist antibody" as suggested by the Examiner.

Accordingly, Applicants respectfully submit that the rejections to claims 4 and 9 under 35 U.S.C. § 112, second paragraph are overcome.

The Rejections to Claims 1-4, 7, 8, 10, and 12-17 under 35 U.S.C. § 102(e)

Claims 1-4, 7, 8, 10, and 12-17 stand rejected under 35 U.S.C. § 102(e) as anticipated by Carnahan, U.S. Patent No. 6,017,886. Carnahan discusses a hybrid peptide (Carnahan SEQ ID NO: 1, shown in Fig. 1 and listed at column 2, lines 5-10 of that reference) and its effects. Carnahan also presents data from experiments on young rat utricular sensory epithelial cells treated with a variety of compounds, including recombinant rat NDFα2, recombinant human NDFα2, and recombinant human NDFβ1 (column 9, lines 55-60).

Anticipation under 35 U.S.C. § 102 requires that "every element of the claimed invention be identically shown in a single reference." (*In re Bond*, 910 F.2d 831,832 (Fed. Cir. 1990).

Applicants respectfully note that the activating ligands of claims 1-4, 7-8, 10, and 12-17 do not include the Carnahan hybrid peptide, nor do they include recombinant rat or human NDFα2 peptides nor recombinant human NDFβ1 peptides. The subject matter of claims 1-4, 7, 8, 10, and 12-17 being directed to activating ligands not discussed in Carnahan, Applicants respectfully submit that these claims are not anticipated by Carnahan. Accordingly, Applicants respectfully submit that the rejection of claims 1-4, 7, 8, 10, and 12-17 under 35 U.S.C. § 102(e) should be withdrawn.

The Objections to claims 5, 6, and 11

Claims 5, 6 and 11 stand objected to as depending from rejected base claims, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 5 and 6 depend from claim 1, and claim 11 depends from claim 6. As discussed above, claim 1 recites subject matter enabled by the specification and not anticipated by Carnahan. Accordingly, Applicants respectfully submit that the objections to claims 5, 6, and 11 are overcome.

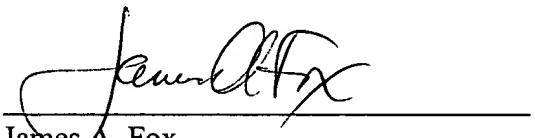
CONCLUSION

In view of the foregoing, it is respectfully submitted that all claims in the present application stand in condition for allowance. Applicants respectfully request reconsideration and allowance of all claims. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

The above amendments are made without acquiescing to any of the arguments presented by the Examiner, and without prejudice to further prosecution of subject matter not covered by the awarded claims in one or more continuing or divisional applications.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641.

Respectfully submitted,



James A. Fox
Registration No. 38,455

Heller Ehrman White & McAuliffe LLP
275 Middlefield Road
Menlo Park, CA 94025-3506
Direct Dial: (650) 324-6951
Facsimile: (650) 324-6654

MARKED-UP VERSION OF THE AMENDMENTS SHOWING CHANGES MADE
(Additions are underlined and deletions are bracketed.)

IN THE SPECIFICATION:

The amendments to the paragraph beginning on page 5, line 14 (paragraph 24):

FIG. 7A-7C show the deduced amino acid sequence (SEQ ID NO:11) and cDNA sequence (SEQ ID NO:12) of γ-HRG. The hydrophobic region is underlined. The EGF-like domain is shaded, cysteine residues in the EGF-like domain are circled. N-linked glycosylation sites are marked above the nucleic acid sequence with a (•).

The amendments to the paragraph beginning on page 27, line 29 (paragraph 152):

Another heregulin variant is γ or gamma-heregulin. γ-HRG is any polypeptide sequence that possesses at least one biological property of native sequence γ-HRG having SEQ ID NO:11. The biological property of this variant is the same as for heregulin noted above. This variant encompasses not only the polypeptide isolated from a native γ-HRG source such as human MDA-MB-175 cells or from another source, such as another animal species, but also the polypeptide prepared by recombinant or synthetic methods. It also includes variant forms including functional derivatives, allelic variants, naturally occurring isoforms and analogues thereof. Sometimes the γ-HRG is "native γ-HRG" which refers to endogenous γ-HRG polypeptide which has been isolated from a mammal. The γ-HRG can also be "native sequence γ-HRG " insofar as it has the same amino acid sequence as a native γ-HRG (e.g. human γ-HRG shown in FIG. 7A-7C). Amino acid sequence variants of the native sequence are prepared by introducing appropriate nucleotide changes into the native sequence DNA, or by in vitro synthesis of the desired polypeptide. Such variants include, for example, deletions from, or insertions or substitutions of, residues within the amino acid sequence shown for the human protein in FIG. 7A-7C as generally described [agove] <u>above</u> for other heregulin. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes

also may alter post-translational processes of the native sequence, such as changing the number or position of O-linked glycosylation sites.

IN THE CLAIMS

1. (Amended) A method of inducing hair cell generation or inner-ear-supporting cell growth, regeneration, and/or proliferation, comprising contacting an inner-ear-supporting cell which expresses HER2 and/or HER3 receptors with an effective amount of an isolated ligand which activates HER2 and/or HER3 receptors [or a combination thereof], said isolated ligand comprising a heregulin polypeptide selected from the group consisting of heregulin-β2 (SEQ ID NO: 5), heregulin-β2-like polypeptide (SEQ ID NO: 9), heregulin-β3 (SEQ ID NO: 7), heregulin γ (SEQ ID NO: 11), heregulin-α (SEQ ID NO: 1) variants, heregulin-β1 (SEQ ID NO: 3) variants, heregulin-β2 (SEQ ID NO: 5) variants, heregulin-β2-like polypeptide (SEQ ID NO: 9) variants, heregulin-β3 (SEQ ID NO: 7) variants, heregulin γ (SEQ ID NO: 11) variants, heregulin-α (SEQ ID NO: 1) fragments, heregulin-β1 (SEQ ID NO: 3) fragments, heregulin-β2 (SEQ ID NO: 5) fragments, heregulin-β2-like polypeptide (SEQ ID NO: 9) fragments, heregulin-β3 (SEQ ID NO: 7) fragments, heregulin γ (SEQ ID NO: 11) fragments, heregulin agonist antibody and heregulin agonist antibody fragments.

2. (Amended) The method of claim 1, wherein the activating ligand is a heregulin-α variant, heregulin agonist antibody or fragment thereof capable of binding to the HER2 or HER3 receptor, wherein said heregulin-α variant is selected from the group of heregulin-α variants having an amino acid substitution, deletion or insertion at one or more amino acid residues corresponding to positions 2, 3, 8, 9, 23, 24, 33, 34, 36, 37, 42, 43, 45, 46, 48, 49, 62-67, 86, 87, 110, 111, 123, 124, 134, 135, 142, 143, 151, 152, 164-166, 170-172, 208-218, 226-254, 256-265, 272, 273, 278, 279, 285-309, 437, and 608- 611 in the heregulin-α amino acid sequence of SEQ ID NO: 1.

3. (Amended) The method of claim [2] 1, wherein the activating ligand is a human heregulin polypeptide or a fragment thereof.

4. (Amended) The method of claim [2] 1, wherein the activating ligand is selected from the group consisting of HRG-α variants, -β1 variants, -β2, -β2 variants, -β2-like polypeptide, -β2-like polypeptide variants, -β3, and -β3 variants, and fragments thereof.

5. (Amended) The method of claim [2] 1, wherein the activating ligand is γ-HRG or a variant or a fragment thereof.

6. (Amended) The method of claim [2] 1, wherein the activating ligand is a recombinant human heregulin polypeptide or a fragment thereof.

7. (Amended) The method of claim [2] 1, wherein the supporting cell is in a cochlear implant.

9. (Amended) The method of claim [2] 1, wherein the activating ligand is [an] a heregulin agonist antibody.

14. (Amended) A method of increasing the number of inner-ear-supporting cells, comprising administering to a patient in need thereof an effective amount of an isolated HER2 and/or HER3 activating ligand comprising a heregulin polypeptide selected from the group consisting of heregulin-β2 (SEQ ID NO: 5), heregulin-β2-like polypeptide (SEQ ID NO: 9), heregulin-β3 (SEQ ID NO: 7), heregulin γ (SEQ ID NO: 11), heregulin-α (SEQ ID NO: 1) variants, heregulin-β1 (SEQ ID NO: 3) variants, heregulin-β2 (SEQ ID NO: 5) variants, heregulin-β2-like polypeptide (SEQ ID NO: 9) variants, heregulin-β3 (SEQ ID NO: 7) variants, heregulin γ (SEQ ID NO: 11) variants, heregulin-α (SEQ ID NO: 1) fragments, heregulin-β1 (SEQ ID NO: 3) fragments, heregulin-β2 (SEQ ID NO: 5) fragments, heregulin-β2-like polypeptide (SEQ ID NO: 9) fragments, heregulin-β3 (SEQ ID NO: 7) fragments, heregulin γ (SEQ ID NO: 11) fragments, heregulin agonist antibody and heregulin agonist antibody fragments.

15. (Amended) The method of claim 14, wherein the activating ligand is a heregulin-α variant, heregulin agonist antibody or fragment thereof capable of binding to the

HER2 or HER3 receptor, wherein said heregulin-α variant is selected from the group of heregulin-α variants having an amino acid substitution, deletion or insertion at one or more amino acid residues corresponding to positions 2, 3, 8, 9, 23, 24, 33, 34, 36, 37, 42, 43, 45, 46, 48, 49, 62-67, 86, 87, 110, 111, 123, 124, 134, 135, 142, 143, 151, 152, 164-166, 170-172, 208-218, 226-254, 256-265, 272, 273, 278, 279, 285-309, 437, and 608- 611 in the heregulin-α amino acid sequence of SEQ ID NO: 1.

16. (Amended) A method of treating a hair cell related hearing disorder, comprising administering to a patient in need thereof an effective amount of an isolated HER2 and/or HER3 activating ligand comprising a heregulin polypeptide selected from the group consisting of heregulin-β2 (SEQ ID NO: 5), heregulin-β2-like polypeptide (SEQ ID NO: 9), heregulin-β3 (SEQ ID NO: 7), heregulin γ (SEQ ID NO: 11), heregulin-α (SEQ ID NO: 1) variants, heregulin-β1 (SEQ ID NO: 3) variants, heregulin-β2 (SEQ ID NO: 5) variants, heregulin-β2-like polypeptide (SEQ ID NO: 9) variants, heregulin-β3 (SEQ ID NO: 7) variants, heregulin γ (SEQ ID NO: 11) variants, heregulin-α (SEQ ID NO: 1) fragments, heregulin-β1 (SEQ ID NO: 3) fragments, heregulin-β2 (SEQ ID NO: 5) fragments, heregulin-β2-like polypeptide (SEQ ID NO: 9) fragments, heregulin-β3 (SEQ ID NO: 7) fragments, heregulin γ (SEQ ID NO: 11) fragments, heregulin agonist antibody and heregulin agonist antibody fragments.

17. (Amended) The method of claim 16, wherein the activating ligand is a heregulin-α variant, heregulin agonist antibody or fragment thereof capable of binding to the HER2 or HER3 receptor, wherein said heregulin-α variant is selected from the group of heregulin-α variants having an amino acid substitution, deletion or insertion at one or more amino acid residues corresponding to positions 2, 3, 8, 9, 23, 24, 33, 34, 36, 37, 42, 43, 45, 46, 48, 49, 62-67, 86, 87, 110, 111, 123, 124, 134, 135, 142, 143, 151, 152, 164-166, 170-172, 208-218, 226-254, 256-265, 272, 273, 278, 279, 285-309, 437, and 608- 611 in the heregulin-α amino acid sequence of SEQ ID NO: 1.